

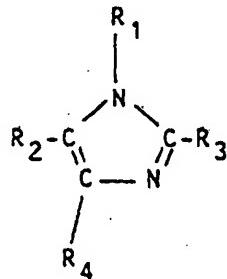


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COMBINATION OF GERMICIDAL AGENTS
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- (56) Prior Art Documents
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- (57) Claim
1. A combination of imidazole and/or one or more derivatives of imidazole which have the following general structural formula



- wherein the radicals have the following meaning:

R₁ = H or C_(1 - 25) - alkyl,

R₂ = H or C_(1 - 25) - alkyl,

R₃ = H or C_(1 - 25) - alkyl,

R₄ = H or C_(1 - 25) - alkyl,

or R₄ is one of the radicals

-CH₂-CH₂-NR₅R₆

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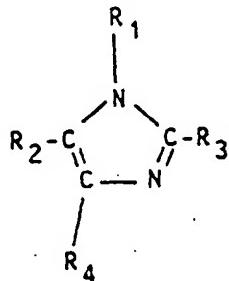
or $-\text{CH}_2-\text{CH}(\text{NR}_5\text{R}_6)-\text{COOR}_7$,

wherein

 $\text{R}_5 = \text{H}$ or $\text{C}_{(1-25)}$ - alkyl, $\text{R}_6 = \text{H}$ or $\text{C}_{(1-25)}$ - alkyl, $\text{R}_7 = \text{H}$ or $\text{C}_{(1-25)}$ - alkyl,

and a lantibiotic or a mixture of two or more lantibiotics,
 the imidazole and lantibiotic being present in an amount
 effective to protect against microorganisms.

13. Use of one or more derivatives of imidazole which have
 the following general structural formula



- wherein the radicals have the following meaning:

 $\text{R}_1 = \text{H}$ or $\text{C}_{(1-25)}$ - alkyl, $\text{R}_2 = \text{H}$ or $\text{C}_{(1-25)}$ - alkyl, $\text{R}_3 = \text{H}$ or $\text{C}_{(1-25)}$ - alkyl, $\text{R}_4 = \text{H}$ or $\text{C}_{(1-25)}$ - alkyl,or R_4 is one of the radicals $-\text{CH}_2-\text{CH}_2-\text{NR}_5\text{R}_6$ or $-\text{CH}_2-\text{CH}(\text{NR}_5\text{R}_6)-\text{COOR}_7$,

wherein

 $\text{R}_5 = \text{H}$ or $\text{C}_{(1-25)}$ - alkyl, $\text{R}_6 = \text{H}$ or $\text{C}_{(1-25)}$ - alkyl, $\text{R}_7 = \text{H}$ or $\text{C}_{(1-25)}$ - alkyl,

for stabilizing lantibiotics.

OPI DATE 29/03/94 APPLN. ID 49509/93
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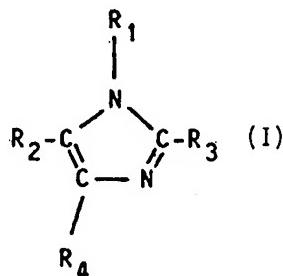
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(54) Title: COMBINATION OF GERMICIDAL AGENTS

(54) Bezeichnung: GERMICIDE WIRKSTOFFKOMBINATIONEN



(57) Abstract

Combinations of imidazol and/or one or more imidazol derivatives with general structural formula (I) in which the residues may be as follows: $R_1 = H, C_{(1-25)}$ alkyl, $R_2 = H, C_{(1-25)}$ alkyl, $R_3 = H, C_{(1-25)}$ alkyl, $R_4 = H, C_{(1-25)}$ alkyl, where R_4 may also, and preferably when R_1, R_2 and R_3 are a hydrogen atom, be the residues $-CH_2-CH_2-NR_5R_6$ and $-CH_2-CH(NR_5R_6)-COOR_7$, where $R_5 = H, C_{(1-25)}$ alkyl, $R_6 = H, C_{(1-25)}$ alkyl, $R_7 = H, C_{(1-25)}$ alkyl, and of a substance active against micro-organisms or a mixture from the lantibiotics group.

(57) Zusammenfassung

Kombinationen aus Imidazol und/oder einem oder mehreren Derivaten des Imidazols, welche die allgemeine Strukturformel (I) aufweisen, wobei die Reste folgende Bedeutung haben können: $R_1 = H, C_{(1-25)}$ - Alkyl, $R_2 = H, C_{(1-25)}$ - Alkyl, $R_3 = H, C_{(1-25)}$ - Alkyl, $R_4 = H, C_{(1-25)}$ - Alkyl bedeuten, wobei R_4 , auch, und zwar bevorzugt dann, wenn R_1, R_2 und R_3 ein Wasserstoffatom darstellen, die Reste $-CH_2-CH_2-NR_5R_6$ und $-CH_2-CH(NR_5R_6)-COOR_7$ repräsentieren kann, wobei $R_5 = H, C_{(1-25)}$ - Alkyl, $R_6 = H, C_{(1-25)}$ - Alkyl, $R_7 = H, C_{(1-25)}$ - Alkyl bedeuten, und einem gegen Mikroorganismen wirksamen Stoff oder einem Gemisch aus der Gruppe der Lantibiotika.

Beiersdorf Aktiengesellschaft**Description****Germicidal active compound combinations**

The present invention relates to active compound
5 combinations for protection against microorganisms. It furthermore relates to formulations, preferably cosmetic and dermatological formulations, in particular cosmetic deodorants, comprising such active compound combinations. It also relates to processes for stabilizing formulations, in particular cosmetic and dermatological formulations, against attack by microorganisms.

10 Active compound combinations for protection against microorganisms are used, for example, in formulations which are applied to the skin or mucous membrane of a person or an animal in order to reduce or eliminate microorganism attack on or in the skin or to prevent attack by microorganisms. Such compositions include the terms topical dermatic agents and cosmetics.

15 However, protection against microorganism attack on formulations themselves, in particular cosmetic and dermatological formulations, is also regarded as protection against microorganisms in the context of the present invention. In technical terms, this protection is called preservation. Preservation in itself is not limited to cosmetic or dermatological formulations. Rather, it relates to protection of all organic materials against microbial degradation.

20 Cosmetic formulations for protection against microorganisms are primarily deodorants, that is to say formulations which are intended to eliminate body odour. Body odour is formed when fresh perspiration, which is in itself odourless, is decomposed by microorganisms. During this operation, a large number of highly volatile substances are formed, malodorous isovaleric acid being mentioned only as an example.



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Deodorants:

Cosmetic deodorants of the prior art are based on various action principles.

The formation of perspiration can be suppressed
5 by astringents - aluminium salts, such as aluminium hydroxychloride, are chiefly used. Apart from the fact that the associated denaturing of skin proteins is an undesirable secondary reaction, the substances used for this purpose furthermore intervene in the heat balance of
10 the skin and should at best be used in exceptional cases.

The bacterial flora on the skin may be reduced by antimicrobial substances. In the ideal case, only the microorganisms causing an odour should be destroyed here. In practice, however, it has been found that the entire
15 microflora of the skin is harmed to the same extent. The microorganisms which cause no odour are occasionally even harmed more severely.

Finally, body odour can also be masked by fragrances, the classical method which, however, meets the aesthetic requirements of the consumer the least, since the mixture of body odour and perfume fragrance smells rather unpleasant.

Deodorants should meet the following conditions:

- (1) The biological processes of the skin should not be impaired.
- 25 (2) The deodorants should not have a pronounced intrinsic smell.
- (3) They must be harmless in the event of an overdose or other use not as specified.
- 30 (4) They should not become concentrated on the skin after repeated use.
- (5) They should be easy to incorporate into commercially available cosmetic formulations.

Both liquid deodorants, for example aerosol sprays, roll-ons and the like, and solid formulations, for example deo sticks, powders, powder sprays, intimate cleansing compositions and the like, are known and customary.

An object of the present invention was thus to



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develop cosmetic deodorants which do not have the disadvantages of the prior art. In particular, the deodorants should largely preserve the microflora of the skin, but selectively reduce the microorganisms which are responsible for body odour.

5 Topical dermotic agents:

Some of the unpleasant or pathogenic germs attack the various layers of the skin, including the acne pathogen Propionibacterium acnes. P. acnes preferentially 10 populates the hair follicles and therefore usually breaks out during puberty of the persons affected. The often considerable skin lesions associated with it are at best unattractive, but may also considerably trouble the patient emotionally.

15 Lantibiotics have also already been proposed as therapeutics against skin complaints caused microbially, namely acne. A disadvantage is that these formulations are stable for only a short time.

20 Another object of the present invention was thus to provide formulations and processes which remedy this shortcoming.

25 Stabilization of perfumed cosmetic formulations:

Cosmetic formulations, that is to say deodorants, having an active content of lantibiotics are known from 25 DE-A 39 38 140. The compositions described therein are distinguished by an outstanding action and tolerability.

30 However, the cosmetic deodorants described therein have the disadvantage that an addition of perfume constituents reduces the deodorizing activity of the lantibiotics in an undesirable manner in a way which has not yet been clarified exhaustively. Since almost all cosmetics, whether deodorizing or not, comprise perfume constituents, this reduction in action represents a considerable problem.

35 Another object of the invention was thus to suppress the harmful action of perfume constituents on active compound components in cosmetic formulations.

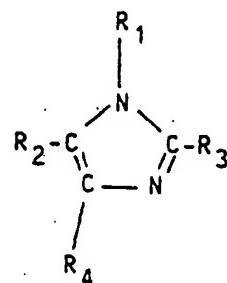
Description of the invention:

It was astonishing and not foreseeable to the



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expert, and herein lies the achievement of all these objects, that combinations of imidazole and/or one or more derivatives of imidazole which can have the following general structural formula



- 5 - wherein the radicals have the following meaning:
 $R_1 = H$ or $C_{(1-25)}$ - alkyl,
 $R_2 = H$ or $C_{(1-25)}$ - alkyl,
 $R_3 = H$ or $C_{(1-25)}$ - alkyl,
10 $R_4 = H$ or $C_{(1-25)}$ - alkyl,
- or R_4 is, and preferably if R_1 , R_2 and R_3 are a hydrogen atom, one of the radicals
 $-CH_2-CH_2-NR_5R_6$
and $-CH_2-CH(NR_5R_6)-COOR_7$,
- 15 wherein
 $R_5 = H$ or $C_{(1-25)}$ - alkyl,
 $R_6 = H$ or $C_{(1-25)}$ - alkyl,
 $R_7 = H$ or $C_{(1-25)}$ - alkyl,
and a lantibiotic or a mixture of two or more
20 lantibiotics,
- would be stable during storage,
- would have a sufficiently high half-life on the skin,
- would be suitable for use as a cosmetic,
25 - do not allow interactions between lantibiotics and perfume constituents,
- would have a suitable stability when used in cosmetics,
- would be active selectively against odour-generating microorganisms,

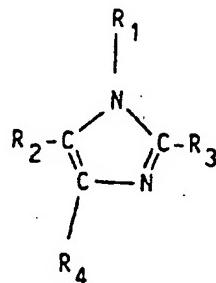


- 5 -

- would preserve the symbiotic microflora of the skin,
- would also be fully active when perfume components are used,
- 5 - would achieve a significant improvement in the deodorizing action compared with imidazole-free compositions,
- would have a suitable stability when used as preservatives,
- 10 - would have a suitable stability when used in foodstuffs.

In particular, it was astonishing that the compositions according to the invention not only are suitable for cosmetic purposes but moreover are more effective and gentler than the compositions of the prior art.

The invention also relates to the use of one or more derivatives of imidazole which have the following general structural formula



- 20 - wherein the radicals can have the following meaning:

$R_1 = H$ or $C_{(1-25)}$, - alkyl,

$R_2 = H$ or $C_{(1-25)}$, - alkyl,

$R_3 = H$ or $C_{(1-25)}$, - alkyl,

25 $R_4 = H$ or $C_{(1-25)}$, - alkyl,

- wherein R_4 can also, and preferably if R_1 , R_2 and R_3 are a hydrogen atom, be the radicals

$-CH_2-CH_2-NR_5R_6$

and $-CH_2-CH(NR_5R_6)-COOR_7$,

wherein



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$R_5 = H$ or $C_{(1-25)}$ - alkyl,

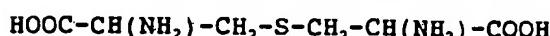
$R_6 = H$ or $C_{(1-25)}$ - alkyl,

$R_7 = H$ or $C_{(1-25)}$ - alkyl,

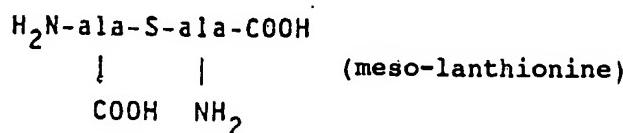
as the active principle in cosmetic deodorants.

5 Lantibiotics per se have been known for many years. They are polypeptides which are synthesized by microorganisms and are distinguished by representatives of the amino acid group of lanthionines as a structural element in the peptide sequence.

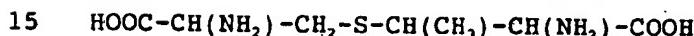
10 The lanthionines have the following structures:



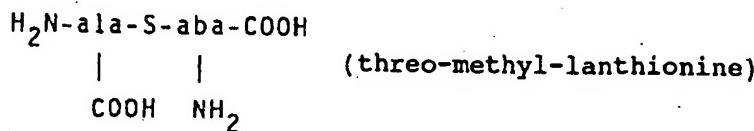
also written as:



and



also written as:



Ring structures are formed in the lantibiotics with these lanthionines.

20 Examples of lantibiotics are nisin, epidermin, subtilin, cinramycin, duramycin, ancovenin, gallidermin and Pep 5.

The abovementioned substances are known per se and can be found under the Chemical Abstracts registry numbers:

25 Nisin : 1414-45-5

Epidermin : 99165-17-0

Subtilin : 1393-38-0

Pep 5 : 110655-58-8

Duramycin : 1391-36-2

Ancovenin : 88201-41-6

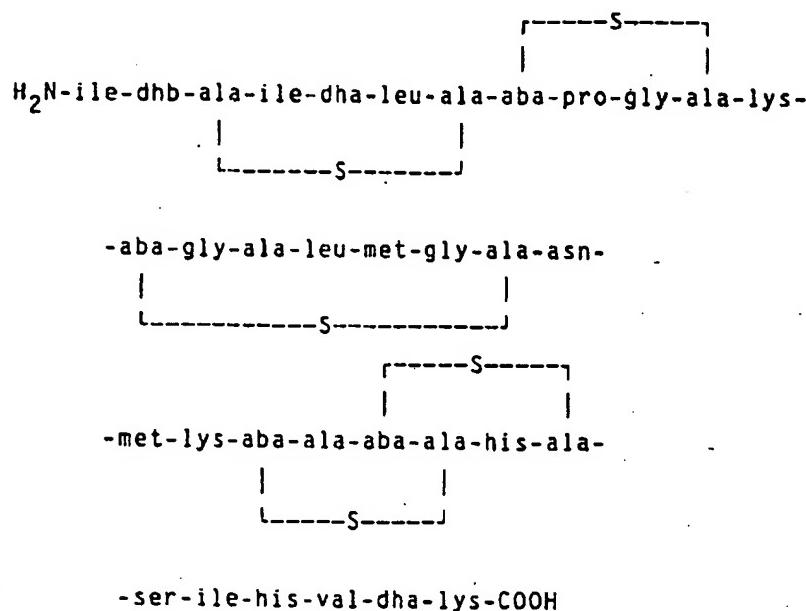


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Gallidermin : 117978-77-5

Nisin, for example, is a peptide of 34 amino acids synthesized by *Streptococcus lactis*.

Nisin has the following amino acid sequence
5 (primary structure):



wherein dhb = dehydrobutyrine

dha = dehydroalanine

aba = aminobutyric acid

E. Gross, J.L. Morell, "The Structure of Nisin", J. Amer. Chem. Soc. 93, pages 4634-4637 (1971).

The action mechanism of nisin and the lantibiotics related to nisin which have essentially the same action can be explained as follows: cell walls are destroyed by release of autolysines. Since channels are also formed in the cytoplasm membrane, low molecular weight cell constituents can diffuse out, whereby the (prokaryotic) cell is destroyed.

The accuracy of this explanation, however, is of no relevance to the invention. An attempt is merely being made to explain the microbiological processes.

Eukaryotic cells, that is to say skin cells.



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fungi and the like, are resistant to nisin and other lantibiotics.

Lantibiotics are practically non-toxic to warm-blooded animals. The LD50 for nisin, for example, is greater than 7 g/kg (determined for rats and cats). It is known that nisin and the other lantibiotics chiefly act against micrococci and coryneform bacteria. In some countries, chiefly in Eastern Europe, it is a substance which is approved as a foodstuffs preservative (not in Germany).

For traditional reasons, lantibiotics are often counted among the so-called "peptide antibiotics". However, for various reasons they are not to be interpreted as conventional antibiotics, at least not all their representatives, least of all nisin. Everything suggests, rather, that they should be given the designation "bacteriocins". Bacteriocins are proteins which are produced by bacteria and kill or inhibit the growth of related bacteria species or strains. They are usually coded by plasmids, the so-called bacteriocin factors.

Epidermin is a lantibiotic which has been isolated from microorganisms occurring on the human skin. The use of epidermin as an antibiotic/therapeutic having a topical action is described in EP-A-0 181 578. It is used for combating infectious diseases.

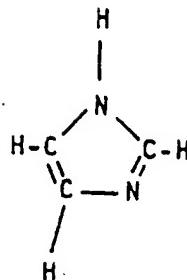
Gallidermin is a lantibiotic which differs from epidermin by only one amino acid. EP-A-0 342 486 cites a cosmetic agent comprising gallidermin, but without cosmetics being disclosed and without the advantageous combination of lantibiotics and imidazole or derivatives thereof being obvious.

International Patent Application WO 89/12399 furthermore discloses combinations of nisin and complexing agents and/or emulsifiers for use as preservatives.

Imidazole is characterized by the structural formula

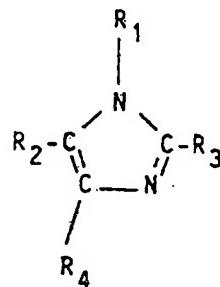


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Imidazole is likewise practically non-toxic to warm-blooded animals, but acts as an antimetabolite against histamine and nicotinic acid in lower animals. Certain derivatives of imidazole are used as antimycotics.

5 Derivatives of imidazole which can likewise be used according to the invention are those of the general structural formula



wherein the radicals can have the following meaning:

R₁ = H or C_(1 - 25) - alkyl,

10 R₂ = H or C_(1 - 25) - alkyl,

R₃ = H or C_(1 - 25) - alkyl,

R₄ = H or C_(1 - 25) - alkyl,

wherein R₄ can also, and preferably if R₁, R₂, and R₃, are a hydrogen atom, be the radicals

15 -CH₂-CH₂-NR₅R₆

and -CH₂-CH(NR₅R₆)-COOR₇,

wherein

R₅ = H or C_(1 - 25) - alkyl,

R₆ = H or C_(1 - 25) - alkyl,

20 R₇ = H or C_(1 - 25) - alkyl.

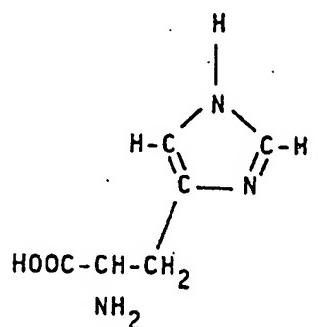
Among these derivatives of imidazole, those which are water- and/or alcohol-soluble are preferred. Those derivatives in which R₁ = H are particularly preferred.



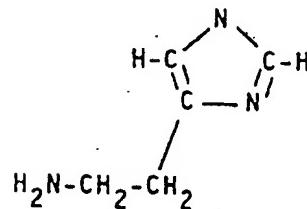
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It is particularly advantageous to use the non-derivatized parent substance ($R_1 - R_4 = H$) of imidazole.

The derivatives histidine



and histamine



5 are also advantageous.

The activity of selected compositions [sic] according to the invention decreases in the following sequence:

Imidazole (unsubstituted) > histamine > histidine

- 10 It is of course clear to the expert that the use of histamine in products which [lacuna] into direct contact with the human or animal organism, that is to say, for example, cosmetics and foodstuffs, would not be acceptable, since histamine, as a tissue hormone, can bring about undesirable reactions: histamine occurs in an increased amount with allergies and anaphylaxes.
- 15

The use of the combination according to the invention of histamine and lantibiotics should therefore be subject to medical supervision.

The combination [sic] according to the invention are advantageously characterized by a content of



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0.01 - 99.99 % by weight of an imidazole component
and

5 99.99 - 0.01 % by weight of an individual substance
or a mixture from the group
of lantibiotics,

based on the total weight of the combination.

The combination [sic] according to the invention
are particularly advantageously characterized by a
content of

10 0.1 - 99.9 % by weight of an imidazole component
and

99.9 - 0.1 % by weight of an individual substance
or a mixture from the group
of lantibiotics,

15 based on the total weight of the combination.

The combination [sic] according to the invention
are especially advantageously characterized by a content
of

20 1.0 - 99.0 % by weight of an imidazole component
and

99.0 - 1.0 % by weight of an individual substance
or a mixture from the group
of lantibiotics,

based on the total weight of the combination.

25 The lantibiotics are preferably present in the
final formulations in concentrations of 0.1 - 10000 ppm.
The lantibiotics are particularly preferably present in

30 the final formulations in concentrations of 0.1 -
750 ppm, especially preferably in concentrations of 0.5 -
400 ppm. The concentration data in each case relate to
the content of pure active compound and to the total
weight of the composition.

35 Formulations having an active content of nisin,
epidermin and/or gallidermin have proved to be particu-
larly advantageous. However, the other lantibiotics
mentioned are also particularly suitable for the use
according to the invention.

It is especially advantageous to use nisin.

It is possible and, where appropriate,



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advantageous to employ a mixture of lantibiotics as the active principle of the compositions according to the invention.

It is particularly advantageous to buffer the 5 compositions according to the invention to a pH range of 2.5 - 6.5. It is particularly favourable to choose the pH in the range of 3.5 - 4.8.

The concentrations of imidazole are advantageously 10 0.01 - 5.00% by weight, based on the total weight of the composition, preferably 0.10 - 2.00% by weight, especially preferably 0.25 - 1.00% by weight.

Compositions which are particularly advantageous are those which comprise combinations having a content of 15 0.1 - 10000 ppm of lantibiotics, in particular nisin, and 0.01 - 5.00 % by weight of imidazole, preferably 2.0 - 750 ppm of lantibiotics, in particular nisin, and 20 0.10 - 2.00 % by weight of imidazole, particularly preferably 5.0 - 400 ppm of lantibiotics, in particular nisin, and 0.25 - 1.00 % by weight of imidazole, 25 in each case based on the total weight of the formulation.

Those formulations which comprise 0.4 - 0.6% by weight of imidazole or derivatives thereof are particularly preferred.

30 Perfume oils which cause lasting deactivation of lantibiotics in particular are listed in Table 1. However, if lantibiotics are present in combination with imidazole or derivatives thereof, the destabilization is compensated.

35 Table 1

Aldehyde C12	Hydroxycitronellol
Allyl amyl glycolate	Isoeugenol
Ambrettolide	Isoraldein 70
Amyl-cinnamaldehyde	Jonol



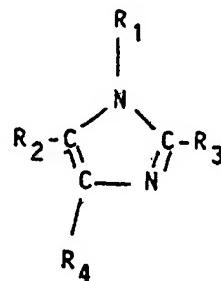
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	Anisaldehyde	Lilial (Firmenich)
	Aurantesin	Lyral
	Benzyl acetate	Methyl dihydrojasmonate
	Benzyl salicylate	Musk ketone
5	Castoreum	p-Hydroxybenzylacetone
	Cedryl ketone	Patchouli oil
	Eugenol	Phenylethyl alcohol
	Florol (Firmenich)	Phenylethyl phenylacetate
	Gamma decalactone	Phenylethyl privalate
10		[sic]
	Geraniol	Tagetes oil
	Geranium oil Bourbon	Terpine oil
	Geranyl acetate	Vertosine
	Helosine	Ylang-ylang-oil
15	Hexenyl salicylate	Zibeth
	Hydrocarboresin	Cinnamaldehyde
	Hydroxycitronellal (Firmenich)	Cinnamyl alcohol

Apart from the perfume oil labelled otherwise,
the perfume oils listed in Table 1 are marketed by the
company Haarmann & Reimer.

Stabilization with respect to the substances
mentioned in Table 1 is claimed according to the invention,
but is not to be limited thereto.

The invention thus also relates to the use of one
25 or more derivatives of imidazole which have the following
general structural formula



- wherein the radicals can have the following
meaning:

R₁ = H or C₍₁₋₂₅₎ = alkyl,



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R₂ = H or C_(1 - 25) - alkyl,

R₃ = H or C_(1 - 25) - alkyl,

R₄ = H or C_(1 - 25) - alkyl,

- wherein R₄ can also, and preferably if R₁, R₂ and R₃ are a hydrogen atom, be the radicals

-CH₂-CH₂-NR₅R₆

and -CH₂-CH(NR₅R₆)-COOR₇,

wherein

R₅ = H or C_(1 - 25) - alkyl,

10 R₆ = H or C_(1 - 25) - alkyl,

R₇ = H or C_(1 - 25) - alkyl,

for stabilizing lantibiotics.

The deodorizing cosmetic compositions according to the invention can be in the form of a preparation which can be sprayed from aerosol containers, squeeze bottles or by a pump device, or in the form of a liquid composition which can be applied by means of roll-on devices, but also in the form of a water-in-oil or oil-in-water emulsion, for example a cream or lotion, which can be applied from normal bottles and containers. Other cosmetic deodorants can be in the form of deodorizing tinctures, deodorizing intimate cleansing compositions, deodorizing shampoos, deodorant soap, deodorizing shower or bath formulations, deodorizing powders or deodorizing powder sprays. However, customary deo stick bases can also serve as carriers for solid formulations and sticks.

Customary cosmetic carrier substances which can be employed for preparation of the deodorizing compositions according to the invention are, in addition to water, ethanol, isopropanol, glycerol and propylene glycol, skincare fatty or fat-like substances, such as partial glycerides of fatty acid mixtures, oleic acid decyl ester, cetyl alcohol, cetyl stearyl alcohol and 2-octyldodecanol, in the ratios of amounts customary for such preparations, as well as mucilaginous substances and thickeners, for example methylcellulose, polyacrylic acid and polyvinylpyrrolidone, and in addition also small amounts of cyclic silicone oils (polydimethylsiloxanes), as well as liquid polymethylphenylsiloxanes of low



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viscosity.

Suitable propellants for deodorizing cosmetic compositions according to the invention which can be sprayed from aerosol containers in the form of a spray jet on actuation of the valve are the customary known highly volatile liquefied propellants, for example hydrocarbons (propane, butane and isobutane), which can be employed by themselves or as a mixture with one another. Compressed air can also advantageously be used, where appropriate.

Emulsifiers which have proved suitable for the preparation of the deodorizing cosmetic compositions according to the invention, which are preferably to be applied to the desired areas of skin as liquid formulations by means of a roll-on device, and can be used in the compositions in a small amount (for example) of 2 to 5% by weight, based on the total composition, are nonionic types, such as polyoxyethylene fatty alcohol ethers, for example cetostearyl alcohol polyethylene glycol ether having 12 or 20 added-on ethylene oxide units per molecule of cetostearyl alcohol, and sorbitan esters and sorbitan ester-ethylene oxide compounds (for example sorbitan monostearate and polyoxyethylene sorbitan monostearate), as well as long-chain higher molecular weight waxy polyglycol ethers.

In addition to the constituents mentioned, it is possible to admix to the deodorizing cosmetic compositions according to the invention - the pH of which is preferably brought to 2.5 to 6.5, in particular 3.5 to 4.8, for example, by customary buffer mixtures - perfume, dyestuffs, antioxidants (for example alpha-tocopherol or butylated hydroxytoluene [sic] (= 2,6-di-tert-butyl-4-methylphenol in amounts of 0.01 to 0.03%, based on the total composition), suspending agents, buffer mixtures or other customary cosmetic base substances, such as triethanolamine or urea.

Those substances and perfume oils which are stable, do not irritate the skin and already have antibacterial (bacteriostatic) properties as such are



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also suitable, where appropriate, for perfuming.

In an individual case, however, it is to be weighed up whether the advantage which the highly selective antimicrobial action of the lantibiotics and, in particular, of the combinations according to the invention offers is to be reduced or not by other substances which, under certain circumstances, have a less selective action.

However, the invention is not limited to the formulations and compositions, auxiliaries and carrier substances mentioned.

The particular amounts of cosmetic carrier substances and perfume to be employed can easily be determined by the expert by simple trials, as a function of the nature of the particular product.

Apart from specific formulations which are noted in each case separately in the examples, the cosmetic compositions are prepared in the customary manner, usually by simple mixing while stirring, if appropriate with gentle heating. The preparation presents no difficulties. For emulsions, the fat phase and the aqueous phase, for example, are prepared separately, if necessary with heating, and then emulsified.

Otherwise, the customary rules for composing cosmetic formulations, with which the expert is familiar, are to be observed.

The combinations according to the invention can be incorporated into the compositions according to the invention in a simple manner. They are preferably added in dissolved form (for example as an aqueous, alcoholic or alcoholic-aqueous solution) to the other constituents of the formulations. However, it is especially advantageous to incorporate lantibiotics into so-called powder sprays. It is also advantageous to avoid additives which can harm the natural microflora, since the combinations according to the invention in themselves selectively reduce the odour-generating microorganisms.

If the combinations according to the invention are to be incorporated into powder sprays, the suspension



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bases for this can advantageously be chosen from the group consisting of aerosil, kieselguhr, kaolin, talc, modified starch, titanium dioxide, zinc oxide, silk powder, nylon powder, 5 polyethylene powder and related substances.

The following examples serve to describe the invention, without the intention being to limit the invention to these examples.

Perfume compositions:

10 Perfume No. 1

Benzyl acetate	4.0% by weight
Geraniol	5.0% by weight
Phenylethyl alcohol	9.0% by weight
Various other odoriferous substances	to 100.0% by weight

15 Perfume No. 2

Benzyl acetate	5.4% by weight
Geraniol	8.0% by weight
Ylang-ylang oil	8.4% by weight
Various other odoriferous substances	to 100.0% by weight

20 Perfume No. 1 [sic]

Benzyl acetate	5.0% by weight
Geraniol	12.0% by weight
Hydroxycitronellal	7.0% by weight
Various other odoriferous substances	to 100.0% by weight

25 Example 1

Pump spray	
Nisin (pure substance)	0.025 g
Imidazole	5.000 g
Ethanol pharm. (96%)	354.875 g
30 Perfume 1	10.000 g
Dyestuff	as desired
Water	to 1,000.000 g

Example 2

Pump spray	
Epidermin	0.010 g
Imidazole	3.500 g
Ethanol pharm. (96%)	354.875 g



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Perfume 1	10.000 g
Dyestuff	as desired
Water	to 1,000.000 g

Example 3

5 Deodorant roller (roll-on)	
Nisin	0.150 g
Imidazole	8.000 g
Hydroxyethylcellulose	5.000 g
Propylene glycol	5.000 g
10 Ethanol pharm. (96%)	355.850 g
Perfume 2	10.000 g
Dyestuff	as desired
Water	to 1,000.000 g

Example 4

15 Deodorant roller (roll-on)	
Epidermin	0.120 g
Imidazole	6.500 g
Hydroxyethylcellulose	5.000 g
Propylene glycol	5.000 g
20 Ethanol pharm. (96%)	355.850 g
Perfume 2	10.000 g
Dyestuff	as desired
Water	to 1,000.000 g

Example 5

25 Spray	
Nisin	0.200 g
Imidazole	1.500 g
Ethanol pharm. (96%)	150.000 g
Propylene glycol	50.000 g
30 Dimethyl ether	300.000 g
Perfume 3	10.000 g
Water	to 1,000.000 g

Example 6

Spray	
Epidermin	0.150 g



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	Imidazole	2.000 g
	Ethanol pharm. (96%)	150.000 g
	Propylene glycol	50.000 g
	Dimethyl ether	300.000 g
5	Perfume 3	10.000 g
	Water	to 1,000.000 g

Example 7

	Spray	
	Nisin	0.180 g
10	Imidazole	17.000 g
	Ethanol pharm. (96%)	497.160 g
	2-Octyldodecanol	2.660 g
	Perfume 1	10.000 g
	Dimethyl ether	to 1,000.000 g

15 Example 8

	Spray	
	Epidermin	0.150 g
	Imidazole	13.800 g
	Ethanol pharm. (96%)	497.160 g
20	2-Octyldodecanol	2.660 g
	Perfume 1	10.000 g
	Dimethyl ether	to 1,000.000 g

Example 9

	Nisin	1.200 g
25	Imidazole	32.000 g
	Cetylstearyl alcohol	20.000 g
	2-Octyldodecanol	20.000 g
	Kaolin	200.200 g
	Talc	200.200 g
30	Aerosil	48.200 g
	Perfume 3	10.000 g
	Rice starch	to 1,000.000 g

Example 10

	Epidermin	1.000 g
	Imidazole	27.000 g



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	Cetylstearyl alcohol	20.000 g
	2-Octyldodecanol	20.000 g
	Kaolin	200.200 g
	Talc	200.200 g
5	Aerosil	48.200 g
	Perfume 3	10.000 g
	Rice starch	to 1,000.000 g

Example 11

	Washing gel concentrate	
10	Nisin	9.000 g
	Imidazole	17.000 g
	Cocoamidopropylbetaine	613.300 g
	Tipa-lauryl ether sulphate	306.700 g
	Sodium chloride	as desired
15	Perfume 2	40.000 g
	Dyestuff	as desired
	Citric acid	1.000 g
	Glycerol	10.000 g
	Water	to 1,000.000 g

20 Example 12

	Washing gel concentrate	
	Epidermin	7.000 g
	Imidazole	12.000 g
	Cocoamidopropylbetaine	613.300 g
25	Tipa-lauryl ether sulphate	306.700 g
	Sodium chloride	as desired
	Perfume 12	40.000 g
	Dyestuff	as desired
	Citric acid	1.000 g
30	Glycerol	10.000 g
	Water	to 1,000.000 g

Example 13

	Powder spray I	
a)	Suspension base	
35	polymethylsiloxane (Cyclomethicone)	72.000 g



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	Talc	24.000 g
	Bentonite gel IPM	3.000 g
	Nisin	1.000 g
	Imidazole	5.000 g
5	Perfume 1	2.500 g

b) Finished spray

	Suspension base I	20.000 g
	Propane/butane	80.000 g

Example 14

10	Powder spray II	
	a) Suspension base	
	Polymethylsiloxane	
	(Cyclomethicone)	72.000 g
	Titanium dioxide	24.000 g
15	Bentonite gel IPM	3.000 g
	Nisin	1.000 g
	Imidazole	8.000 g
	Perfume 3	2.000 g

b) Finished spray

20	Suspension base I	20.000 g
	Propane/butane	80.000 g

Example 15

	Powder spray III	
	a) Suspension base	
25	Polymethylsiloxane	
	(Cyclomethicone)	72.000 g
	Silk powder	24.000 g
	Bentonite gel IPM	3.000 g
	Nisin	1.000 g
30	Imidazole	6.000 g
	Perfume 2	2.000 g

b) Finished spray

	Suspension base I	20.000 g
	Propane/butane	80.000 g



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The superiority of the present invention is demonstrated with the aid of the following experiments. The compositions according to the examples were evaluated with the aid of the so-called "sniff test".

5 Experiment 1:

Compositions according to the invention from Example 1 were tested against a placebo, that is to say a composition which is identical apart from the content of active substance.

10 A group of 30 subjects were told to treat in each case one armpit with composition according to the invention and the other with placebo. The subjects then wore a shirt with slip inserts under the shoulders for three hours. After this period of time, the slip inserts were
15 transferred to separate bottles. The smell of the inserts was evaluated by three test persons. The experiment was carried out as a double-blind experiment, so that neither the subjects nor the test persons knew which armpit had been treated with which composition.

20 It was found that the formulations containing active compound had a better action when evaluated sensorially than the corresponding placebos in each case in 29 out of 30 cases. In 1 out of 30 cases the test person stated that the treated and untreated samples did
25 not differ from one another.

Experiment 2:

30 Compositions from Example 4 (comprising imidazole, formulations C) according to the invention were tested against compositions identical to these without imidazole (formulations D).

35 A group of 30 subjects were told to treat in each case one armpit with formulation C and the other with formulation D. The subjects then wore a shirt with slip inserts under the shoulders for three hours. After this period of time, the slip inserts were transferred to separate bottles. The smell of the inserts was evaluated by five test persons. The experiment was carried out as a double-blind experiment, so that neither the subjects nor the test persons knew which armpit had been treated



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with which composition.

It was found that the formulations C had a better action when evaluated sensorially than formulations D in each case in 25 out of 30 cases.

5 In each case in 4 out of 30 cases, formulations D were evaluated as being better sensorially than formulations C.

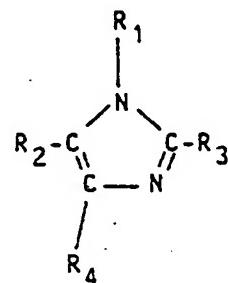
In 1 out of 30 cases, the test person stated that the treated and untreated samples did not differ from one
10 another.



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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A combination of imidazole and/or one or more derivatives of imidazole which have the following general structural formula



- 5 - wherein the radicals have the following meaning:

$R_1 = H$ or $C_{(1 - 25)}$ - alkyl,

$R_2 = H$ or $C_{(1 - 25)}$ - alkyl,

$R_3 = H$ or $C_{(1 - 25)}$ - alkyl,

$R_4 = H$ or $C_{(1 - 25)}$ - alkyl,

10 or R_4 is one of the radicals

$-CH_2-CH_2-NR_5R_6$

or $-CH_2-CH(NR_5R_6)-COOR_7$,

wherein

$R_5 = H$ or $C_{(1 - 25)}$ - alkyl,

15 $R_6 = H$ or $C_{(1 - 25)}$ - alkyl,

$R_7 = H$ or $C_{(1 - 25)}$ - alkyl,

and a lantibiotic or a mixture of two or more lantibiotics, the imidazole and lantibiotic being present in an amount effective to protect against microorganisms.

- 20 2. A combination according to claim 1 wherein R_1 , R_2 and R_3 are hydrogen atoms and R_4 is $-CH_2-CH_2-NR_5R_6$ or $-CH_2-CH(NR_5R_6)-COOR_7$.



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3. A combination according to claim 1 or 2 wherein the lantibiotics are chosen from the group consisting of nisin, epidermin, subtilin, cinramycin, duramycin, ancovenin, Pep 5 and gallidermin.
- 5 4. A combination according to any one of claims 1 to 3, wherein the imidazole derivatives are chosen from the group consisting of unsubstituted imidazole, histidine and histamine..
5. A combination according to any one of claims 1 to 4,
10 characterized by a content of

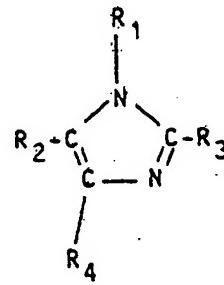
0.01 - 99.99 % by weight of an imidazole component and

99.99 - 0.01 % by weight of an individual substance or
a mixture from the group of lantibiotics, based on the
total weight of the combination.
- 15 6. A formulation comprising a combination according to any
one of claims 1 to 5, wherein the lantibiotic(s) are
present in a content of 0.1 - 10000 ppm, based on the total
weight of the formulation.
7. A formulation comprising a combination according to any
20 one of claims 1 to 5, wherein the lantibiotic(s) are
present in a content of 0.1 - 750 ppm, based on the total
weight of the formulation.
8. A formulation comprising a combination according to any
one of claims 1 to 5, wherein the lantibiotic(s) are
25 present in a content of 0.5 - 400 ppm, based on the total
weight of the formulation.



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9. A formulation comprising a combination according to any one of claims 1 to 5, wherein the imidazole derivative or derivatives are present in a concentration of 0.01 - 5.00% by weight, based on the total weight of the formulation.
- 5 10. A formulation comprising a combination according to any one of claims 1 to 5, wherein the imidazole derivative or derivatives are present in a concentration of 0.10 - 2.00% by weight, based on the total weight of the formulation.
11. A formulation comprising a combination according to any 10 one of claims 1 to 5, wherein the imidazole derivative or derivatives are present in a concentration of 0.4 - 0.6% by weight, based on the total weight of the formulation.
12. A formulation comprising a combination according to any one of claims 1 to 11, characterized in that they are in 15 the form of deodorant sprays, roll-ons, pump sprays, tinctures, intimate cleansing compositions, shampoos, shower or bath formulations, powders, powder sprays or deo sticks.
13. Use of one or more derivatives of imidazole which have 20 the following general structural formula



- wherein the radicals have the following meaning:
R₁ = H or C_(1 - 25) - alkyl,



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$R_2 = H$ or $C_{(1 - 25)}$ - alkyl,
 $R_3 = H$ or $C_{(1 - 25)}$ - alkyl,
 $R_4 = H$ or $C_{(1 - 25)}$ - alkyl,
or R_4 is one of the radicals

5 $-CH_2-CH_2-NR_5R_6$
or $-CH_2-CH(NR_5R_6)-COOR_7$,

wherein

10 $R_5 = H$ or $C_{(1 - 25)}$ - alkyl,
 $R_6 = H$ or $C_{(1 - 25)}$ - alkyl,
 $R_7 = H$ or $C_{(1 - 25)}$ - alkyl,

for stabilizing lantibiotics.

14. Use according to claim 13 wherein R_1 , R_2 and R_3 are hydrogen atoms and R_4 is $-CH_2-CH_2-NR_5R_6$ or $-CH_2-CH(NR_5R_6)-COOR_7$.

15 15. Use of combinations according to any one of claims 1 - 4 for combating *Propionibacterium acnes*.

16. Use of combinations according to any one of claims 1 - 4 for the preparation of a dermatological formulation against acne.

20 17. A combination substantially as herein described with reference to any one of Examples 1 to 15.

DATED this 17th day of June, 1996

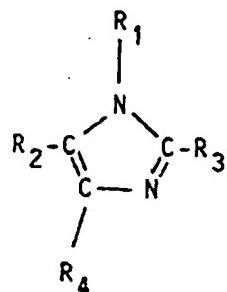
BBEIERSDORF AG

25 Attorney: RUTH M. CLARKSON
Fellow Institute of Patent Attorneys of Australia
of SHELSTON WATERS



Abstract

Combinations of imidazole and/or one or more derivatives of imidazole which have the following general structural formula



- wherein the radicals can have the following meaning:

R₁ = H or C_(1 - 25) - alkyl,

R₂ = H or C_(1 - 25) - alkyl,

R₃ = H or C_(1 - 25) - alkyl,

R₄ = H or C_(1 - 25) - alkyl,

- wherein R₄ can also, and preferably if R₁, R₂ and R₃ are a hydrogen atom, be the radicals

-CH₂-CH₂-NR₅R₆

and -CH₂-CH(NR₅R₆)-COOR₇,

wherein

R₅ = H or C_(1 - 25) - alkyl,

R₆ = H or C_(1 - 25) - alkyl,

R₇ = H or C_(1 - 25) - alkyl,

and a substance which is active against microorganisms or a mixture from the group of lantibiotics.



INTERNATIONAL SEARCH REPORT

Later national Application No
PCT/EP 93/02238

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A01N63/02 A61K7/32 A61K7/48 // (A01N63/02, 43:50, 25:22)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 451 002 (BRISTOL-MYERS) 9 October 1991 see claims 1,2 ---	13
X	EP,A,0 274 267 (UNILEVER) 13 July 1988 see page 5, line 15 - line 28 ---	13
A	WO,A,91 07164 (BEIERSDORF) 30 May 1991 see claims & DE,A,39 38-140 cited in the application -----	1-12

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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1

Date of the actual completion of the international search

19 November 1993

Date of mailing of the international search report

03.12.93

Name and mailing address of the ISA
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DECORTE, D

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 93/02238

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0451002	09-10-91	AU-B-	634643	25-02-93
		AU-A-	7403591	10-10-91
		JP-A-	5097641	20-04-93
EP-A-0274267	13-07-88	AU-B-	602039	27-09-90
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		DE-A-	3780607	27-08-92
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		AU-A-	6617290	13-06-91
		EP-A-	0500605	02-09-92
		JP-T-	5501875	08-04-93
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		WO-A-	9107164	30-05-91
		EP-A-	0500605	02-09-92
		JP-T-	5501875	08-04-93

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP 93/02238

A. KLASIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
 IPK 5 A01N63/02 A61K7/32 A61K7/48 // (A01N63/02, 43:50, 25:22)

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

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Recherchierte Mindestprüfstoff (Klassifikationssystem und Klassifikationsymbole)
 IPK 5 A01N A61K

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Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	EP,A,0 451 002 (BRISTOL-MYERS) 9. Oktober 1991 siehe Ansprüche 1,2 ---	13
X	EP,A,0 274 267 (UNILEVER) 13. Juli 1988 siehe Seite 5, Zeile 15 - Zeile 28 ---	13
A	WO,A,91 07164 (BEIERSDORF) 30. Mai 1991 siehe Ansprüche & DE,A,39 38 140 in der Anmeldung erwähnt -----	1-12

 Weitere Veröffentlichungen und der Fortsetzung von Feld C zu entnehmen Siche Anhang-Patentfamilie

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Datum des Abschlusses der Internationalen Recherche	Absendedatum des internationalen Recherchenberichts
19. November 1993	03.12.93

Name und Postanschrift der Internationale Recherchenbehörde
 Europäisches Patentamt, P.B. 5818 Patentlaan 2
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Bevollmächtigter Bediensteter

DECORTE, D

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen

PCT/EP 93/02238

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
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EP-A-0274267	13-07-88	AU-B- 602039 AU-A- 8281187 CA-A- 1306198 DE-A- 3780607	27-09-90 23-06-88 11-08-92 27-08-92
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DE-A-3938140	08-08-91	AU-A- 6617290 WO-A- 9107164 EP-A- 0500605 JP-T- 5501875	13-06-91 30-05-91 02-09-92 08-04-93

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